REMARKS

Claims 1-7 and 10-13 are pending in the present application. Claims 11-13 have been withdrawn. No claim amendments have been made.

Restriction Requirement

The Office has requested that the Applicants clarify their traversal of the June 23, 2008 restriction requirement. In its requirement for restriction, the Office noted that if the Applicants elected Group I, claims 1-7 and 10, for prosecution at this time, that a further restriction would be made according to structures (a-1) – (a-8). The Applicants maintain their traversal of the further restriction requiring a species election.

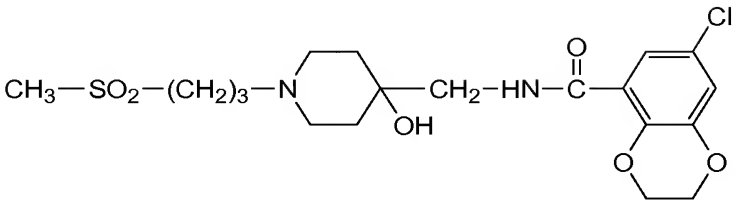
The restriction of Markush-type claims is governed by MPEP 803.02. "[I]t is improper for the Office to refuse to examine that which applicants regards as their invention, unless the subject matter in a claim lacks unity of invention. Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature essential to that utility." MPEP 803.02. The Applicants assert that the claims fulfill the requirements for unity of invention.

Indeed, the Written Opinion of the International Searching Authority identified that unity of invention does exist for the pending claims. Moreover, as indicated in Applicants' previous response, the Office Action's assertion that at least one Markush alternative is not novel over WO 00/37461 is erroneous and does not support lack of unity. Withdrawal of the requirement for further restriction is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 1-7 and 10 stand rejected under 35 U.S.C. § 103 as allegedly obvious over U.S. 6,544,997 (Bosmans) in view of Lima, supplemented with Supuran, Chavatte, or Penning, further in view of U.S. 4,186,135 (Thominet). The Applicants disagree and request reconsideration and withdrawal of the rejection.

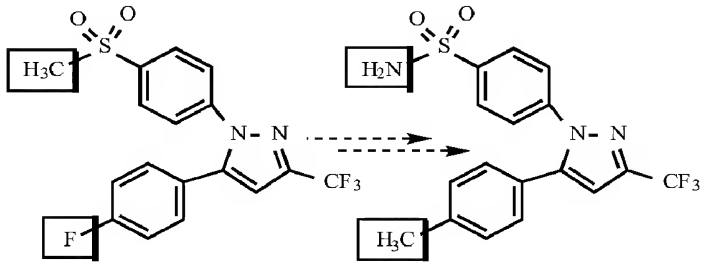
The Office has identified Compound 103, set forth at col. 43-44 in Bosmans, as the closest prior art:



Compound 103, Bosmans

As acknowledged by the Office, among the differences between Compound 103 and the claimed invention is the L substitutent. The claimed invention includes compounds wherein L is –Alk-SO_2-**NH_2**. Compound 103 of Bosmans has an –Alk-SO_2-**CH_3** substitution. The Office alleges that the prior art teaches that –SO_2-NH_2 and –SO_2-CH_3 are bioisosteric and that one skilled in the art would have been motivated to replace the –SO_2-CH_3 of Bosmans with the –SO_2-NH_2 of the present invention. The Office has mischaracterized the teachings of the art and has failed to properly set forth a *prima facie* case of obviousness.

Lima summarizes Penning. Specifically, Lima describes two cyclooxygenase-2 (COX-2) inhibitors prepared in Penning:



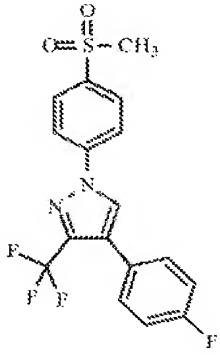
29 **30**

$t_{1/2}$ = 211h $t_{1/2}$ = 8 a 12 h

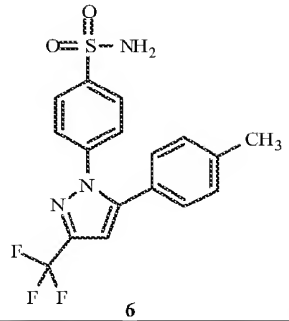
SI (COX-2/COX-1) = >1000 SI (COX-2/COX-1) = 375

As set forth in Lima, Compound 29, while very selective for COX-2 over COX-1 (SI COX-2/COX-1 > 1000), had a half life that was considered too long for the particular pharmaceutical use ($t_{1/2}$ – 211 h). The –SO_2-CH_3 of Compound 29 was replaced with –SO_2-NH_2 to produce Compound 30. ***In addition***, the fluorine of Compound 29 was replaced with –CH_3. Compound 30 is much less selective for COX-2 over COX-1 (SI COX-2/COX-1 = 375) and it has a significantly shorter half life ($t_{1/2}$ – 8-12 h), as compared to Compound 29.

Supran describes the following COX-2 inhibitor compounds, **5** and **6**:



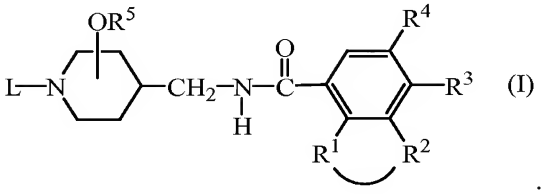
5 (SC 58125)



6 (Celecoxib)

Supuran describes that the biological activities of **5** and **6** as to CA inhibition are different. *See* Supuran Table 1. Similar COX-2 inhibitors are described in Chavatte.

The compounds of Bosmans and the present invention ***are not*** described as COX inhibitors; rather, the compounds of Bosmans and the present invention are described as $5HT_4$ antagonists. Furthermore, the compounds of the present invention are compounds of Formula I:



(I)

The compounds of Bosmans have a core structure similar to claims Formula I. Formula I is structurally distinct from the diphenyl pyrazoles described in Lima, Penning, Supuran, and Chavatte.

One of skill in the art would not have combined the $5HT_4$ antagonists of Bosmans with the COX-2 inhibitors of Lima, Penning, Supuran, or Chavatte because the biological targets are distinct. Moreover, the core structure of the compounds of Bosmans is distinct from the dephenyl pyrazoles of Lima, Penning, Supuran, and Chavatte; therefore, one skilled in the art could not have predicted that the replacement of the $-SO_2-CH_3$ of Bosmans with the $-SO_2-NH_2$ of the cited art would have provided a compound suitable for use as a $5HT_4$ antagonist. Indeed, based on the Office's application of the cited art, the replacement with $-SO_2-NH_2$ resulted in a compound that has a significantly shorter half life and is less selective for the biological target.

The Applicants further assert that the Office's reliance on the cited art to support the alleged bioisosteric equivalency of $-SO_2-CH_3$ and $-SO_2-NH_2$ is scientifically inappropriate. As stated in Lima, Penning made ***two*** chemical modifications in Compound 30 - the $-SO_2-CH_3$ of Compound 29 was replaced with $-SO_2-NH_2$ ***and*** the fluorine of Compound 29 was replaced with $-CH_3$. It is therefore impossible to attribute any change or similarity in biological activity solely to the $-SO_2-CH_3$ replacement without taking into account the fluorine replacement. The Office has failed to address the impact of the fluorine replacement.

The citation of Thominet does not cure the deficiencies of Bosmans and Lima, Penning, Supuran, and Chavatte. Applicants respectfully request withdrawal and reconsideration of the rejection under § 103.

Obviousness-type double patenting rejections

Claims 1-7 and 10 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-3 and 5-8 of Bosmans in view of Lima, supplemented with Supuran, Chavatte, or Penning. In light of the remarks made above, reconsideration and withdrawal of the rejection is requested.

Claims 1-7 and 10 stand provisionally rejection on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-7 and 10 of U.S. App. No. 10/560,479 or claims 1-7 and 10 of U.S. App. No. 10/560,485 or claims 1-7 and 10 of U.S. App. No. 10/560,486 in view of Lima supplements with Supuran, Chavette, or Penning. In view of the remarks made above, reconsideration and withdrawal of the rejection is requested.

The Applicants assert that the foregoing constitutes a full and complete response to the November 10, 2008 Office Action and that claims 1-7 and 10 are in condition for allowance. Rejoinder of claims 11-13 is hereby requested.

Date: March 4, 2009

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